Title Page

(1) Title:

The Histological Evaluation of Therapeutic Effect and RCB (residual cancer burden) index in Primary Breast Cancer Operated After Neo-adjuvant Chemotherapy.

- Retrospective study of the clinic-pathological findings and prognosis -

(2) Names of all authors:

Seiya Hajikano1) , Yuko Hirota2) , Nobukazu Shima1) , Reika Suzuki3) , Terumasa Sawada4) , Seigo Nakamura4) , Nobuyuki Oike3) , Haruhiro Inoue5) , Masafumi Takimoto1)

(3) Institutions and departments:

1) Department of Pathology and Laboratory Medicine, Showa University School of Medicine

2) Diagnostic pathology, Showa university Koto Toyosu hospital

3) Diagnostic pathology, Showa university Fujigaoka hospital

4) Breast surgical oncology, Showa university hospital

5) Digestive disease Center, Showa university Koto Toyosu hospital

(4) Name and address of corresponding author:

Seiya Hajikano

1-5-8, Hatanodai, Shinagawa-Ku, Tokyo, 142-8555, Japan

E-mail: seiya-haji@hotmail.co.jp

Tel: 03-3784-8119 Fax: 03-3784-8249

(5) Running title:

The Histological Evaluation of Therapeutic Effect with RCB (residual cancer burden) index in Primary Breast Cancer Operated After Neo-adjuvant Chemotherapy.

Abstract

The histological therapeutic effect seen after surgery following NAC is said to relate to the prognosis of the patient .We need to consider not only invasive lesions remained, but also intra-ductal components or lymph node metastasis. We used the RCB index and compared it with the conventional method of judging the histopathological therapeutic effect. We also investigated the clinico-pathological features as well as recurrence and the prognosis by the RCB index.

We studied 244 cases of primary breast cancer in 238 patients who had undergone surgery after NAC in Showa university hospital between 2005 and 2014. We classified the cases into groups based on the Japanese Breast Cancer Society's criteria for evaluating the histological therapeutic effect and the RCB index. The cases were analyzed in regard to various clinico-pathological factors. The prognosis was evaluated by drawing recurrence-free survival curves using the Kaplan-Meier method, and the log rank test was

used to analyze for statistical significance.

We evaluate the RCB index values for cases of Grade 0–1b that had a certain degree of residual tumor tissue.

Comparison of the recurrence-free survival rates in each of the RCB index groups indicated a significant correlation.

A significant correlation between the RCB index and the recurrence-free survival period, only for patients with some degree of residual malignancy even after chemotherapy. We think that the RCB index can be used for carrying out more precise prediction of recurrence.

Key Words:

Breast cancer, Neoadjuvant chemotherapy (NAC),

RCB (residual cancer burden) index, pathology, surgery

1. Introduction

Patients with invasive breast cancer that is operable show similar survival whether they undergo surgery following neoadjuvant chemotherapy (NAC) or have surgery first and then receive chemotherapy 1–3). Also, the histological therapeutic effect seen in surgical specimens following NAC is said to relate to the prognosis of the patient, and long-term survival is obtained especially in patients diagnosed as having achieved pathological complete response (pCR) 2)4). A meta-analysis of 12 recent clinical studies of NAC for breast cancer reported that pCR can serve as a surrogate endpoint for event-free survival (EFS) and/or overall survival (OS)5). In general, the most commonly used criteria for histological evaluation are the diagnostic criteria of Fisher et al. that were employed in the NSABP B-18 study4). It was assumed that no invasive lesions remained, and intra-ductal components or lymph node metastasis of cancers were not taken into account. Then, in the later NSABP B-27 study, evaluation of intraductal

components was performed in addition to the diagnostic criteria of Fisher et al. 6). Recently, it has been said that evaluation of the residual presence of lymph node metastases should also be performed 5). We therefore consider that the histological evaluation criteria must be decided upon. Needless to say, the objectivity and reproducibility of histological evaluations will be very important in such determinations.

The residual cancer burden (RCB) index proposed by Symmans et al. 7) has been used in numerous large-scale clinical studies, including I-SPY (1,2), GEICAM, ACOSOG (Z11103), CALGB (40601, 40603), NSABP (B-40, B-41), and ABCSG (34), and its reproducibility has been evaluated 8). Based on this background, we used the RCB index and compared it with the conventional method of judging the histopathological therapeutic effect, that is, by evaluating the status of residual invasive lesions. We also investigated the clinico-pathological features as well as recurrence and the prognosis by the RCB index.

2. Materials and Methods

1) Methods

The subjects of this study were 244 cases of primary breast cancer in 238 patients who had undergone surgery after NAC in Showa university hospital between 2005 and 2014. All the subjects were women, and 6 patients had bilateral synchronous breast cancer.

We collected the clinical and pathological information of the study subjects and created a database. We performed a retrospective survey of the medical records regarding postoperative recurrence and death. We classified the cases into 2 groups (Grade 0, 1a, 1b, 2a and Grade 2b, 3) based on the Japanese Breast Cancer Society's criteria for evaluating the histological therapeutic effect. And we also classified them into 2 groups (RCB -0, 1 and RCB-2, 3) after calculating the RCB index for each case. The cases were analyzed in regard to various clinico-pathological factors including age, clinical stage, histological type, vascular invasion, lymph node metastasis, biomarkers, chemotherapy regimen, surgical

procedure, recurrence, death, etc. We analyzed them by using t-test and chi-square test. And the prognosis was evaluated by drawing recurrence-free survival curves using the Kaplan-Meier method, and the log rank test was used to analyze for statistical significance.

The biomarker findings were classified as follows: ≥10% ER•PgR was defined as positive, for HER2 only score 3 was considered positive, and ≥30% Ki67 was defined as positive.

2) About the Japanese Breast Cancer Society's criteria

The Japanese Breast Cancer Society's criteria classifies cases into groups of Grade 0 to Grade 3 based on evaluation the histological therapeutic effect (Table 6) 9).

3) About RCB index

The extent of residual disease (RD) in the post-treatment surgical resection specimen could be determined from bidimensional diameters of the primary tumor bed in the resection specimen

($d_1$and d_2), the proportion of the primary tumor bed that contains invasive carcinoma (f_{inv}), the number of axillary lymph nodes containing metastatic carcinoma (LN), and the diameter of the largest metastasis in an axillary lymph node (d_{met}). If multiple tumors were present, the dimensions of the largest were recorded. Bidimensional measurements of the primary tumor bed (millimeters) were combined as follows:

$$d_{prim} = \sqrt{d_1 d_2}$$

The proportion of invasive carcinoma (f_{inv}) within the cross sectional area of the primary tumor bed was estimated from the overall percent area of carcinoma ($\%CA$) and then corrected for the component of in situ carcinoma ($\%CIS$):

$$f_{inv} = (1 - (\%CIS/100)) \times (\%CA/100)$$

From the above, they defined RCB index as follows:

$$\text{RCB} = 1.4(f_{inv} d_{prim})^{0.17} + [4(1 - 0.75^{LN}) d_{met}]^{0.17}$$

They identified two cutoff points to assign patients with RD (not RCB-0) after NAC into one of three classes: RCB-1 (minimal RD), RCB-2 (moderate RD), and RCB-3 (extensive RD). Two cutoff

points were determined sequentially by maximizing the profile log-likelihood of a multivariate Cox model that included the clinical covariates and the dichotomized RCB index. The first cutoff point (RCB-3 and RCB-1/2) was selected as the 87th percentile (RCB, 3.28), and the second (RCB-1 and RCB-2) corresponds to the 40th percentile (RCB, 1.36) 7).

3. Results

Data on patients background characteristics for the 244 cases are compiled in Table 1. The mean patient age was 51.6 years, and the mean duration of follow-up was 30.5 (6-120) months. Recurrence was seen in 38 cases, and 11 cases died. The mean time from surgery until recurrence was 28.2 months, and the mean time until death was 46.1 months.

About the pretreatment stage of the cases, no striking differences were found in the distributions of the disease stage in each group when using the criteria for evaluating the histological therapeutic effect according to the General Rules for Clinical and Pathological Recording of Breast Cancer or when using the RCB index (Table 2).

Table 3 shows data for the clinico-pathological factors for each of the histological therapeutic effect evaluation criteria of the General Rules for Clinical and Pathological Recording of Breast Cancer. There was a tendency for the diameter of invasive tumor and the degree of vascular invasion and lymph node metastasisto

increase as the percentage of residual invasive lesions increased. Stratification of the biomarker findings indicated that, compared with the overall distributions, Grade 0, 1a, 1b, 2a showed a tendency for more ER(+), HER2(-), ki67<30% cases, while Grade 2a, 3 showed a tendency for more ER(-), HER2(+) and ER(-), HER2(-), ki67≥30% cases. In addition, the rates of recurrence and death were low in Grade 2b, 3, specifically 7.7% and 0.0%, respectively, whereas their rates were 17.7% and 5.8% in Grade 0, 1a, 1b, 2a. But there were not significant differences.

Next, Table 4 shows the results of stratification of the clinico-pathological factors for each RCB index group. Stratification of the biomarker findings indicated that, compared with the overall distributions, RCB-0, 1 showed a tendency for more cases of ER(-), HER2(+), while RCB-2, 3 showed a tendency for more cases of ER(+), HER2(-), ki67<30%. In addition, about the rates of recurrence and death, there were not significant differences between 2 groups.

We drew the recurrence-free survival plots (Figure 3). The left plot

shows the curves for the Grade 0, 1a, 1b, 2a and Grade 2a, 3 groups based on the histological therapeutic effect evaluation criteria of the Japanese Breast Cancer Society. The right plot shows the curves for the RCB-0, 1 and RCB-2, 3 groups based on the RCB index. The recurrence-free survival plots were compared, but the analyses did not find statistically significant differences (p=0.1236 and p=0.0645).

Table 5 presents the results of stratification of the clinic-pathological factors for each RCB index groups for cases of Grade 0–1b that had a certain degree of residual tumor tissue, after excluding the cases of pCR and nearly pCR, which are considered to have a good prognosis. Stratification of the biomarker findings indicated that the percentage of ER(+), HER2(-), ki67<30% cases tended to increase as the RCB index increased, whereas, conversely, the percentage of ER(+), HER2(+), ki67<30% cases tended to decrease. About the rates of recurrence and death, there were not significant differences between 2 groups.

We drew the recurrence-free survival plots for cases of Grade 0–1b

that had a certain degree of residual tumor tissue (Figure 4). This plot shows the curves for the RCB-1 and RCB-2, 3 groups based on the RCB index for cases of Grade 0–1b. Comparison of the recurrence-free survival rates in each of the RCB index groups indicated a significant correlation ($p=0.0483^*$).

From the results, for cases that had a certain degree of residual tumor tissue, RCB index can be used for carrying out prediction of the outcomes. In addition, it is considered that we can treat the cases of RCB-1 group almost equally to RCB-0 (pCR).

4. Discussion

In this study, we used the RCB index as a means for evaluating the status of residual tumors and investigated the histological therapeutic effect based on the criteria of the General Rules for Clinical and Pathological Recording of Breast Cancer, the clinical histopathological data, recurrence and the prognosis.

Reports to date have identified various prognostic factors in patients who have undergone surgery following NAC. Those factors include the clinical stage, histological type, tumor diameter, axillary lymph node metastasis, vascular invasion, a multifocal pattern of residual tumors, tumor necrosis, hormone receptors, positive rate of HER2, ki67 cells, menopausal status, race (African-American), etc. 10–15). About hormone receptors, positive rate of HER2, ki67 cells, we resulted in the same conclusion to the past reports. Concretely, the cases they had good effects of NAC showed a tendency for more cases in which estrogen receptor was negative, HER2 was positive, and Ki-67 was high.

Most of those reports have rated the tumor diameter and axillary lymph node metastasis as the most important prognostic factors 10–13). A recent report stated that it is better to use T0 N0 or T0/is N0 as the definition of pCR 5). In our present paper, we used the RCB index, which not only takes into consideration of the primary lesion and axillary lymph node metastasis, but may also be a more accurate prognostic index since it is a numerical rating.

Table 6 shows the other criteria used for evaluating the histological therapeutic effect16).

The RCB index that we used has been employed in numerous clinical studies 8). In addition, the reproducibility of the RCB index has been evaluated as high, with an RCB category concordance rate of 0.989 8). As important items that should be included in pathology reports, one report stated pCR/non-pCR, the T stage, N stage, and RCB index if not available, 2 perpendicular diameters of the tumor 17).

Our present results found a significant correlation between the RCB index and the recurrence-free survival period, only for

patients with some degree of residual malignancy even after chemotherapy. We think that the RCB index can be used for carrying out more precise prediction of recurrence. However, the RCB index did not show a significant correlation with survival. Noting that the mean 5-year survival was in excess of 90% for stage II breast cancer 18), for which chemotherapy is indicated, it is difficult to claim that a mean follow-up period of 30.5 months is even close to being sufficient. Thus, the issue of the duration of follow-up warrants further investigation.

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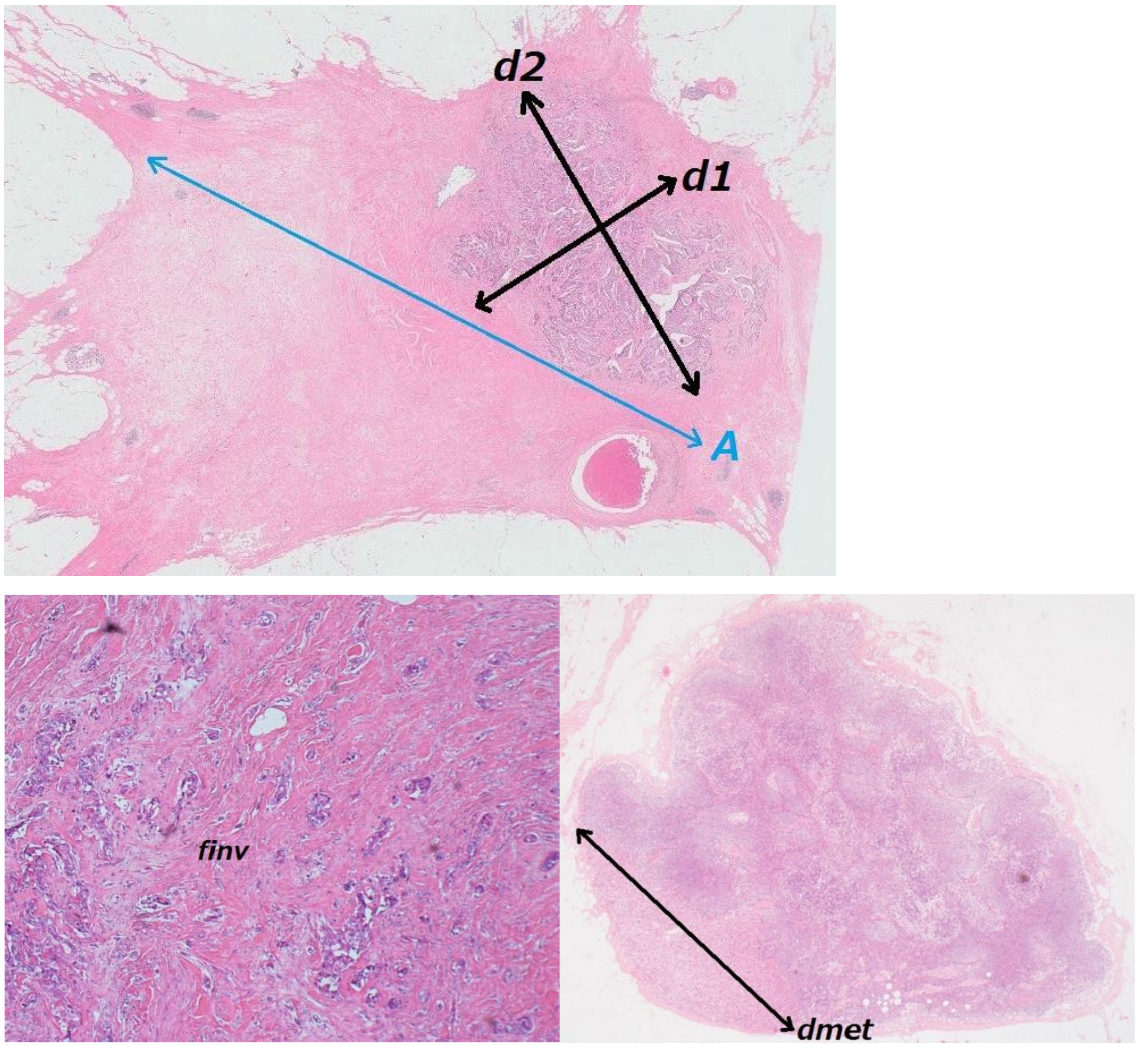
Figure Legends and Tables

Figure 1 : RCB index



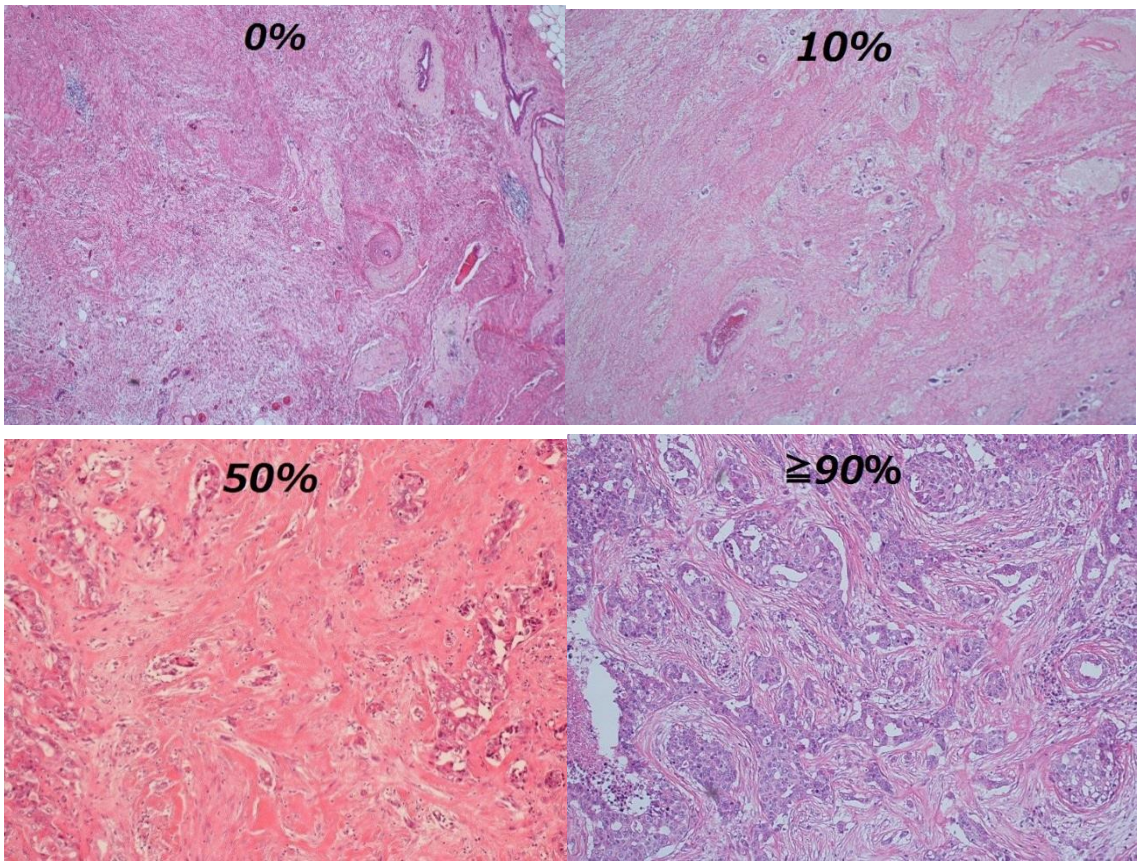
$$\mathrm{RCB} = 1.4(f_{inv} \; d_{prim})^{0.17} + [4(1 - 0.75^{LN})d_{met}]^{0.17}$$

$$d_{prim} = \sqrt{d_1 d_2}$$

$$f_{inv} = (1 - \; (\%CIS/100)) \times (\%CA/100)$$

The pathological variables included bidimensional diameters of the primary tumor bed (d1, d2), the proportion of primary tumor area containing invasive carcinoma (finv), the number of positive lymph nodes (LN), and the diameter of the largest nodal metastasis (dmet). The diameter is considered that the tumor was exist before NAC (A). The proportion of invasive carcinoma (finv) within the cross sectional area of the primary tumor bed was estimated from the overall percent area of carcinoma (%CA) and then corrected for the component of in situ carcinoma (%CIS).

Figure 2 : The overall percent area of carcinoma (%CA)



We evaluated the overall percent area of carcinoma (%CA) like these figures to calculate RCB index.

Table 1 : Patient background characteristics

		n=244					
Age	Mean (Range)	51.6 (26-74)		Chemotherapy	FEC	9	
T stage	T1	60	24.6%		FEC→PTX (+Her)	67 (+9)	
	T2	124	50.8%		FEC→DTX (+Her)	88 (+31)	
	T3	22	9.0%		FEC→TC +Her	1	
	T4	36	14.8%		FEC→GEM+Carboplatin	4	
	Uncertain	2	0.8%		Bev+PTX	3	
N stage	N0	137	56.1%		Pertuzumab+DTX +Her	2	
	N1	97	39.8%		Bev+PTX+Eribulin	1	
	N2	3	1.2%		DTX+CPA +HER	1	
	N3	5	2.0%		TC (+Her)	12 (+5)	
	Uncertain	2	0.8%		PTX (+Her)	5 (+1)	
M stage	M(+)	3	1.2%		DTX	3	
	M(-)	239	98.0%		Uncertain	2	
	Uncertain	2	0.8%	Operation	Partial resection	111	45.5%
Histlogic type	IDC	227	93.0%		Total resection	133	54.5%
	Special type	17	7.0%	Recurrence	None	206	84.2%
Biomarker	ER(+)	138	56.6%		Local recurrence	2	1.0%
	ER(-)	97	39.8%		Distant recurrence	36	14.8%
	Uncertain	9	3.6%	Death	None	233	95.3%
	PgR(+)	106	43.4%		Death with recurrence	10	4.3%
	PgR(-)	127	52.0%		Death of other disease	1	0.4%
	Uncertain	11	4.6%		(Lung metastasis of overian cancer)		
	HER2(+)	58	23.8%				
	HER2(-)	177	72.5%				
	Uncertain	9	3.7%				
	Ki67(+)	106	43.4%				
	Ki67(-)	93	38.1%				
	Uncertain	45	18.5%				

Table 2 : The pretreatment stage of the cases

	T					N					M		
	T1	T2	T3	T4	Uncertain	N0	N1	N2	N3	Uncertain	M(+)	M(−)	Uncertain
Grade 0,1	38	76	13	25	1	83	65	2	2	1	2	150	1
153	24.8%	49.7%	8.5%	16.3%	0.7%	54.2%	42.5%	1.3%	1.3%	0.7%	1.3%	98.0%	0.7%
Grade 2	11	25	5	6	0	31	16	0	0	0	0	47	0
47	23.4%	53.1%	10.6%	12.8%	0.0%	66.0%	34.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Grade 3	11	23	4	5	1	23	16	1	3	1	1	42	1
44	25.0%	52.3%	9.1%	11.4%	2.3%	52.3%	36.4%	2.3%	6.8%	2.3%	2.3%	95.4%	2.3%
RCB−0	9	20	4	4	1	22	13	1	1	1	0	37	1
38	23.7%	52.6%	10.5%	10.5%	2.6%	57.9%	34.2%	2.6%	2.6%	2.6%	0.0%	97.4%	2.6%
RCB−1	14	25	6	5	1	36	13	0	1	1	1	49	1
51	27.5%	49.0%	11.8%	9.8%	2.0%	70.6%	25.5%	0.0%	2.0%	2.0%	2.0%	96.0%	2.0%
RCB−2	29	60	9	17	0	69	44	1	1	0	1	114	0
115	25.2%	52.2%	7.8%	14.8%	0.0%	60.0%	38.3%	0.9%	0.9%	0.0%	0.9%	99.1%	0.0%
RCB−3	8	19	3	10	0	10	27	1	2	0	1	39	0
40	20.0%	47.5%	8.7%	25.0%	0.0%	25.0%	67.5%	2.5%	5.0%	0.0%	2.5%	97.5%	0.0%
All cases	60	124	22	36	2	137	97	3	5	2	3	239	2
244	24.6%	50.8%	9.0%	14.8%	0.8%	56.1%	39.8%	1.2%	2.0%	0.8%	1.2%	98.0%	0.8%

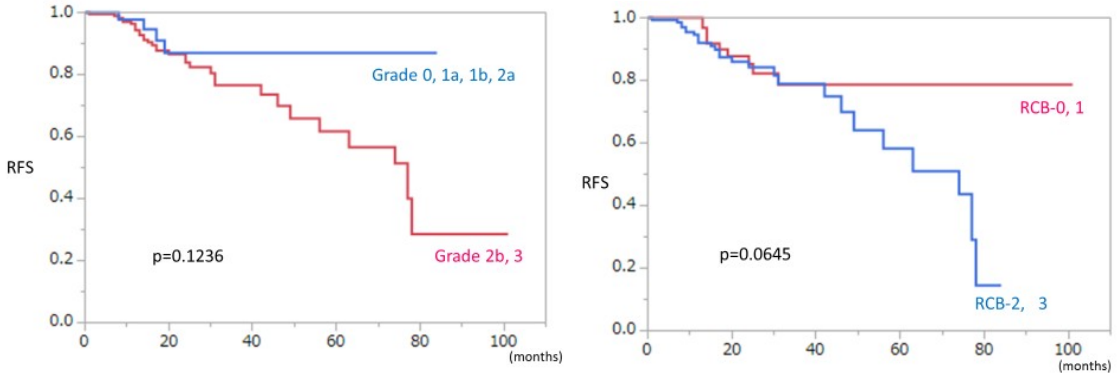
Table 3 : The clinico-pathological data of Grade 0, 1a, 1b, 2a and Grade 2b,3 group

			All cases		Grade 0, 1, 2a		Grade 2b, 3		*p value*
			244		192 (78.7%)		52 (21.3%)		<0.05
Age	Mean (Range)		51.6 (26–74)		52.1 (26–74)		51 (34–71)		0.2176
Tumor diameter (mm)	Mean (Range) (mm)		17.9 (0–105)		22.1 (0–105)		0.09 (0–3)		<0.0001*
Vessel invasion	ly (+)		29	11.9%	29	15.1%	0	0.0%	0.0023*
	v (+)		3	1.2%	3	1.6%	0	0.0%	0.3644
Lymph node metastasis	N (+)		82	33.6%	78	40.6%	0	0.0%	<0.0001*
Biomarker	ER+, HER2−	ki67≧30%	31	12.7%	26	13.5%	5	9.6%	0.4508
		ki67<30%	68	27.9%	66	34.4%	2	3.8%	<0.0001*
		Uncertain	16	6.6%	16	8.3%	0	0.0%	
	ER+, HER2+	ki67≧30%	11	4.5%	8	4.2%	3	5.8%	0.6213
		ki67<30%	9	3.7%	6	3.1%	3	5.8%	0.3695
		Uncertain	3	1.2%	3	1.6%	0	0.0%	
	ER−, HER2+	ki67≧30%	21	8.6%	10	5.2%	11	21.2%	0.0003*
		ki67<30%	6	2.5%	2	1.0%	4	7.7%	0.0060*
		Uncertain	8	3.3%	6	3.1%	2	3.8%	
	ER−, HER2−	ki67≧30%	43	17.6%	28	14.6%	15	28.8%	0.0166*
		ki67<30%	10	4.1%	10	5.2%	0	0.0%	0.0929
		Uncertain	9	3.7%	5	2.6%	4	7.7%	
	Uncertain		9	3.7%	6	3.1%	3	5.8%	
Recurrence	−		206	84.4%	158	82.3%	48	92.3%	
	+		38	15.6%	34	17.7%	4	7.7%	0.0772
Death	−		233	95.5%	181	94.2%	52	100.0%	
	+		11	4.5%	11	5.8%	0	0.0%	0.0773
Observation period	Mean(Range) (Months)		30.5 (6–120)		31.6 (6–120)		28.1 (6–93)		0.4842

Table 4 : The clinico-pathological data of RCB-0, 1 and RCB-2, 3 group

			All cases		RCB-0, 1		RCB-2, 3		*p value*
			244		89, 36.5%		155, 63.5%		<0.05
Age	Mean (Range)		51.6 (26-74)		51.8 (31-74)		51.5 (26-74)		0.9809
Tumor diameter (mm)	Mean (Range) (mm)		17.9 (0-105)		4.47 (0-35)		27.1 (0-105)		<0.0001*
Vessel invasion	ly (+)		29	11.9%	2	2.2%	27	17.4%	0.0013*
	v (+)		3	1.2%	0	0.0%	3	1.9%	0.1866
Lymph node metastasis	N (+)		82	33.6%	2	2.2%	80	51.6%	<0.0001*
Biomarker	ER+, HER2-	ki67≧30%	31	12.7%	11	12.4%	20	12.9%	0.6016
		ki67<30%	68	27.9%	7	7.9%	61	39.4%	<0.0001*
		Uncertain	16	6.6%	3	3.4%	13	8.4%	
	ER+, HER2+	ki67≧30%	11	4.5%	4	4.5%	7	4.5%	0.9937
		ki67<30%	9	3.7%	6	6.7%	3	1.9%	0.0552
		Uncertain	3	1.2%	0	0.0%	3	1.9%	
	ER-, HER2+	ki67≧30%	21	8.6%	14	15.7%	7	4.5%	0.0026*
		ki67<30%	6	2.5%	5	5.6%	1	0.6%	0.0158*
		Uncertain	8	3.3%	7	7.9%	1	0.6%	
	ER-, HER2-	ki67≧30%	43	17.6%	20	22.5%	23	14.8%	0.132
		ki67<30%	10	4.1%	2	2.2%	8	5.2%	0.2691
		Uncertain	9	3.7%	5	5.6%	4	2.6%	
	Uncertain		9	3.7%	5	5.6%	4	2.6%	
Recurrence	−		206	84.4%	78	87.6%	128	82.6%	
	+		38	15.6%	11	12.4%	27	17.4%	0.2941
Death	−		233	95.5%	86	93.3%	147	94.2%	
	+		11	4.5%	3	6.7%	8	5.8%	0.5164
Observation period	Mean(Range) (Months)		30.5 (6-120)		31.3(6-120)		29.9(8-110)		0.3378

Figure 3 : The recurrence-free survival (RFS) plots

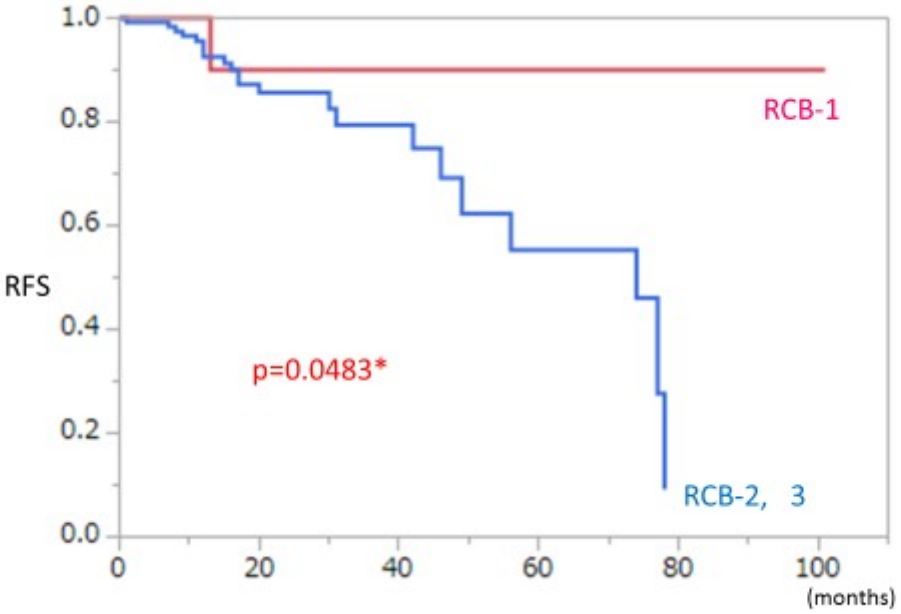


This figures show the recurrence-free survival (RFS) plots. The left plot shows the curves for the Grade 0, 1a, 1b, 2a and Grade 2b, 3 groups based on the histological therapeutic effect evaluation criteria of the Japanese Breast Cancer Society, while the right plot shows the curves for the RCB-0, 1 and RCB-2, 3 groups based on the RCB index. The recurrence-free survival plots were compared, but the analyses did not find statistically significant differences (P=0.1236 and P=0.0645).

Table 5 : The clinico-pathological data of RCB-0, 1 and RCB-2, 3 group for cases of Grade 0–1b

			Grade 0–1b		RCB–1		RCB–2, 3		*p value*
			153		17, 11.1%		136, 88.9%		<0.05
Age	Mean (Range)		52.3	(31–74)	57.2	(38–74)	51.7	(31–74)	0.1037
Tumor diameter (mm)	Mean (Range) (mm)		27.2	(1–105)	11.8	(1–35)	29.2	(4–105)	<0.0001*
Vessel invasion	ly (+)		24	15.7%	2	11.8%	22	16.2%	0.6928
	v (+)		3	2.0%	0	0.0%	3	2.2%	0.5641
Lymph node metastasis	N (+)		69	45.1%	0	0.0%	69	50.7%	0.0002*
Biomarker	ER+, HER2−	ki67≧30%	19	12.4%	3	17.6%	16	11.8%	0.9099
		ki67<30%	59	36.8%	2	11.8%	57	41.9%	0.0075*
		Uncertain	14	5.7%	2	11.8%	12	8.8%	
	ER+, HER2+	ki67≧30%	5	3.3%	0	0.0%	5	3.7%	0.4535
		ki67<30%	5	3.3%	2	11.8%	3	2.2%	0.021*
		Uncertain	1	0.7%	0	0.0%	1	0.7%	
	ER−, HER2+	ki67≧30%	6	3.9%	0	0.0%	6	4.4%	0.41
		ki67<30%	1	0.7%	0	0.0%	1	0.7%	0.7408
		Uncertain	2	1.3%	1	5.9%	1	0.7%	
	ER−, HER2−	ki67≧30%	22	14.4%	1	5.9%	21	15.4%	0.3701
		ki67<30%	8	5.2%	1	5.9%	7	5.1%	0.7922
		Uncertain	5	3.3%	3	17.6%	2	1.5%	
	Uncertain		6	3.9%	2	11.8%	4	2.9%	
Recurrence	−		129	84.3%	16	94.1%	113	83.1%	
	+		24	15.7%	1	5.9%	23	16.9%	0.3118
Death	−		147	96.1%	17	100.0%	130	95.6%	
	+		6	3.9%	0	0.0%	6	4.4%	0.41
Observation period	Mean (Range) (Months)		30.4	(6–120)	37.2	(9–120)	30	(6–110)	0.0755

Figure 4 : The recurrence-free survival (RFS) plots for cases of Grade 0–1b



This figure shows the recurrence-free survival (RFS) plots. This plot shows the curves for the RCB-1 and RCB-2, 3 groups based on the RCB index for cases of Grade 0–1b.Comparison of the recurrence-free survival rates in each of the RCB index groups indicated a significant correlation (p=0.0483*).

Table 6 : The other criteria used for evaluating the histological therapeutic effect

	Year	Criteria for evaluating the histological therapeutic effect		
The Japanese Breast Cancer Society's criteria	2012	Grade 0 (No Response)		Presence of little change in cancer cells
		Grade 1 (Partially Effective)	1a (Mild Effect)	Pleasence of changes in cancer cells inspite of the area, or severe changes in less than 1/3 cancer cells
			1b (Moderate Effect)	Presence of severe changes in more than 1/3 and less than 2/3 cancer cells
		Grade 2 (Quite Effective)	2a (High Effect)	Presence of severe changes in more than 2/3 cancer cells, but presence of cancer nest clearly
			2b (Extremely High Effect)	Presence of effect nearly Complete Response (Grade 3), but presence of extremely a little cancer cells
		Grade 3 (Complete Response)		Presence of necrosis, disappearance or replacement of glomerous or fibrous tissue in all cancer cells
NSABP B-18 criteria	1997	pCR	No recognizable invasive tumor cells present	
		pPR	The presence of scattered individual or small clusters of tumor in a desmoplastic or hyaline stroma	
		pNR	Tumors not exhibiting the changes listed above	
Chevallier's grading system	1993	Class 1 (pCR)	Disappearance of all tumor	
		Class 2 (pCR)	Presence of DCIS in the breast, no invasive carcinoma and negative lymph node	
		Class 3 (pPR)	Presence of invasive carcinoma with stromal alteration	
		Class 4 (pNR)	Few modifications of the tumoral appearance	
Miller-Payne's grading system	2003	Grade 1 (pNR)	No change or some alteration to individual malignant cells, but no reduction in overall cellularity	
		Grade 2 (pPR)	A minor loss of tumor cells, but overall cellularity still high ; up to 30 % loss	
		Grade 3 (pPR)	Between an estimated 30% and 90% reduction in tumor cells	
		Grade 4 (almost pCR)	A marked disappearance of tumor cells such that only small clusters or widely dispersed indivisual cell remains ; >90% loss of tumor cells	
		grade 5 (pCR)	No malignant cells identifiable in sections from the site of the tumor ; only vascular fibroelastotic dstroma remains, often containing macrophages ; however, ductal carcinoma in situ may be present	
Sataloff's grading system	1995	Tumor T-A	Total or near total therapeutic effect (pCR)	
		T-B	>50% therapeutic effect, but less than total or near total (pPR)	
		T-C	<50% therapeutic effect, but effect evident (pPR)	
		T-D	No therapeutic effect (pNR)	
		Node N-A	Evidence of therapeutic effect, no metastatic disease	
		N-B	No nodal metastasis or therapeutic effect	
		N-C	Evidence of therapeutic effect, but nodal metastatasis present	
		N-D	Viable metastatic disease, no therapeutic effect	